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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHONG, KIMBERLY	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,229	RANA, TARIQ M.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-34* is/are pending in the application.

4a) Of the above claim(s) *18-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-17* is/are rejected.

7)☒ Claim(s) *15-17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/12/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/12/2009 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 01/12/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/11/2007 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 12/11/2007, claims 2-34 are pending in the application. Claims 2-17 are currently under examination.

New Claim Objections

Claims 15-17 are objected to because of the following informalities: Claim 15 recites the limitation "the siRNAi" and it appears to have misspelled "siRNA". Claims 16

and 17 are objected to because they depend from claim 15. Appropriate correction is required.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-8 and 10-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ecker et al. (US Patent No. 5,965,722 of record cited on PTO Form 892 filed 04/02/2007), ten Asbroek et al. (Nucleic Acids Research 2000, Vol. 28: 1133-1138), Hojo et al. (Eur Respir J, 1998 of record cited on PTO Form 892 filed 04/02/2007), Hammond et al. (Nature Reviews Genetics, 2001 of record cited on PTO Form 892 filed 04/02/2007), Bass et al (Nature, 2001 of record cited on PTO Form 892 filed 04/02/2007) and Tuschl et al. (cited on PTO Form 892 filed 11/15/2005).

The claims are drawn to a siRNA comprising a sense strand and an antisense strand wherein the antisense strand comprises a modified base positioned opposite at least one point mutation in the first allele and wherein the modified base is capable of enhancing binding interactions, wherein the sense strand comprises a sequence homologous to a mutant allele encoding a gain-of-function mutant protein, wherein the modified base is selected from the group as listed in claim 4, wherein the point mutation

is an adenine or thymine, wherein the siRNA is from 10-50, 20-40, 18-25 nucleotides in length and drawn to a composition and a host cell comprising said siRNA.

Ecker et al. teach antisense compounds targeted to a mutated Ras gene and teach said antisense compounds are a useful tool for understanding the role of various oncogenes (see column 3). Ecker et al. teach antisense compounds comprising modified nucleotide bases increase the affinity for base mismatches in mutated genes and further enhance the compounds selectivity for such mutated genes (see column 3). Ecker et al. teach a single nucleotide mutation is responsible for mutated Ras protein expression (see column 3). Ecker et al. teach incorporation of a 2'amino adenine at the position that is complementary to the uracil of the mutated codon serves to stabilize the hybridization of the antisense oligonucleotide to the mutated gene (see column 21, lines 40-45). Ecker et al. further teach incorporation of a 2, 6-diamino adenosine complementary to the uracil of the mutated codon was also found to be effective in increasing the hybridization of the antisense compound to the mutated gene (see column 21, lines 55-65). Ecker et al. teach compositions comprising said antisense compound that are useful for therapeutic applications and further teach expression of said antisense compounds in cells (see column 22).

ten Asbroek et al. teach using antisense compounds targeted to one mutant allele of a pair that is vital to cell growth and viability of the cancer cell. ten Asbroek et al. identified single nucleotide polymorphisms in gene that are vital to the cancer cell growth and designed antisense compounds that can selectively discriminate between these mutant genes and wild type genes for allele-specific inhibition (see entire

document and page 1135 Figures 1, 2 and 3). ten Asbroek et al. teach this is an efficient therapeutic approach to cancer therapy to kill mutant cancer cells and teach efficient methods of designing antisense compounds that selectively target the mutant allele compare to the wild type allele wherein the mutant allele differs from the wild-type by one nucleotide (see page 1133). Neither Ecker et al. nor ten Asbroek et al. teach siRNA targeted to a mutated gene and do not teach the point mutation is an adenine or thymine.

Hojo et al. teach a common problem with diseases such as lung cancer are found to be due to overexpression of the p53 and further teach overexpression of p53 is due to point mutations of the p53 gene wherein the mutations are commonly an adenine or a thymidine.

Tuschl et al. disclose a method of inhibiting the expression of a cellular gene that is a tumor gene (a mutant target gene), in vitro in a mammalian cell comprising introducing a dsRNA molecule and maintaining the cell for a time sufficient to obtain degradation of an RNA transcript (see page 7 lines 25-32 and page 8, lines 20-25). Tuschl et al. further disclose the dsRNA of their invention can be a 19-25 nucleotide duplex (see page 3, lines 22-26), the dsRNA has sufficient identity to a nucleic acid target molecule (see page 6, lines 7-11) and teach compositions comprising siRNA and an acceptable carrier (see page 9, lines 17-25). Tuschl et al. teach that siRNAs represent a new alternative to antisense or ribozyme therapeutics. Tuschl et al. teach the siRNA may contain at least one modified analogue, such as a modified base wherein the modified base comprises 5-bromouracil or 5-iodouracil and the dsRNA

structures contain mismatches (page 4, lines 29-32 to page 5, lines1-3). On page 50, it is taught that target recognition is a highly sequence-specific process mediated by the siRNA complementary to the target and Tuschl et al. found that nucleotides in the center of the siRNA strand are important specificity determinants and even a single nucleotide change can reduce RNAi to undetectable levels. From this discovery, Tuschl et al. teach siRNA duplexes can discriminate between mutant or polymorphic alleles which are important in therapeutic developments involving said mutant alleles.

It would have been obvious to one of ordinary skill in the art to design siRNA molecules that are capable of allele-specific targeting, as taught by Tuschl et al. to target mutant alleles, particularly in cancer cells such as caused by p53 and provide sequence specific degradation.

At the time of filing of the instant application, it was well known in the art that dsRNAs were emerging as a more efficient technology for silencing gene expression. Hammond et al. teach two methods for silencing specific genes: antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "...questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach " "...dsRNAs have been shown to inhibit gene expression in a sequence-specific manner" and further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression." Similarly, Bass et al. states that RNA interference using siRNA has "...repeatedly proven itself to be more robust than antisense techniques: It works more often, and typically decreases expression of a

gene to lower levels, or eliminates it entirely." Bass et al. points out that siRNAs are effective at targeting transgenes as well as naturally occurring endogenous genes (see page 428). Bass et al. further states "...siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments."

Moreover, it was well known at the time of filing of the instant invention regarding the desirability to target a mutant allele in a pair of alleles wherein the mutant allele is responsible for the progression of certain diseases, such as cancer. As stated above, both Ecker et al. and ten Asbroek et al. identified single nucleotide polymorphisms in genes that are vital to the cancer cell growth and demonstrated sequence specific inhibitory compounds to target and reduce expression from the mutant allele as compared to the wild-type allele. Ecker et al. and ten Asbroek et al. have both shown that targeting mutant alleles and reducing expression from said allele is a promising therapeutic approach to treating certain diseases and because siRNAs were emerging as the new preferred class of inhibitory molecules to silence gene expression, it would have been obvious to make siRNA to target mutant alleles. One of skill in the art would have clearly looked to the teachings of Tuschl et al. to make siRNA given Tuschl et al. provide specific guidelines to make siRNA to any target gene and would have wanted to design a siRNA that is capable of distinguishing a mutant allele over the wild type gene given Tuschl et al. discloses that siRNA duplexes can discriminate between mutant or polymorphic allele. Tuschl et al. teach on pages 49 and 50 that single mutations within the center of a siRNA strand can discriminate between mismatched targets.

In efforts to improve the specificity of the siRNA to the mutant target gene, one would have wanted to make a siRNA wherein the antisense strand, the strand that binds to the target gene, comprises a modified base because Ecker et al. specifically teach incorporation of modified bases increase the specificity of the nucleic acid to the mismatched base. One of skill in the art would have wanted to incorporate modifications to siRNA to improve the affinity for target genes because siRNA encounters similar problems as other nucleic acid based therapies such as antisense and a person of ordinary skill in the art has good reasons to pursue the known options, as taught by Ecker et al., within his or her technical ability. One of skill in the art would have been further motivated to make a siRNA targeted to a mutated p53 because Hojo et al. teach that overexpression of p53 is responsible for the complications in lung cancer and one would have been motivated to decrease the expression of p53. Hojo et al. demonstrates, for example, that it is the nature of the mutated target that would determine the base that is opposite the modified base of the nucleic acid based drug.

Ecker et al. and ten Asbroek et al. provide evidence that one of skill in the art would have had a reasonable expectation of success at targeting and reducing expression of a mutant target gene using inhibitory molecules and given that Tuschl et al. teach how to make and use any siRNA targeted to any gene, Hammond et al. and Bass et al teach siRNA are preferred over antisense compounds, one would have had a reasonable expectation of success at making a siRNA targeted to a mutated gene.

Thus, in absence of evidence to the contrary, the invention would have been prima facie obvious to one of skill in the art

Claims 2-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klug et al. (European Journal of Physiology 2001, cited on IDS filed 11/20/2007), Ecker et al. (US Patent No. 5,965,722 of record cited on PTO Form 892 filed 04/02/2007), Hammond et al. (Nature Review Genetics, 2001 of record cited on PTO Form 892 filed 04/02/2007), Bass et al (Nature, 2001 of record cited on PTO Form 892 filed 04/02/2007) and Tuschl et al. (cited on PTO Form 892 filed 11/15/2005).

The claims are drawn to a siRNA comprising a sense strand and an antisense strand wherein the antisense strand comprises a modified base positioned opposite at least one pint mutation in the first allele and wherein the modified base is capable of enhancing binding interactions, wherein the sense strand comprises a sequence homologous to a mutant allele encoding a gain-of-function mutant protein, wherein the modified base is selected from the group as listed in claim 4, wherein the siRNA targets a disorder such as ALS, Huntington's, Alzheimer's or Parkinson's, wherein the siRNA is from 10-50, 20-40, 18-25 nucleotides in length an drawn to a composition and a host cell comprising said siRNA.

Klug et al. teach a point mutation, G93A, in a SOD1 gene causes a toxic effect that is responsible for ALS disease. Klug et al. teach an antisense compound that is selective against said point mutation that is capable of inhibiting expression of said gene as compared to the wild-type gene (see entire abstract). Klug et al. do not teach siRNA targeted to a gene correlated with a disease selected from ALS, Huntington's disease, Alzheimer' disease or Parkinson's Disease and do not teach wherein the antisense

strand comprises a modified base positioned opposite at least one pint mutation in the first allele and wherein the modified base is capable of enhancing binding interactions.

Ecker et al. teach sequence antisense compounds capable of discriminating between a mutated Ras gene as compared to the wild-type gene (see column 3) amd teach that antisense compounds comprising modified nucleotide bases opposite the point mutation increase the affinity for base mismatches in mutated genes and further enhance the compounds selectivity for such mutated genes (see column 3). Ecker et al. teach a single nucleotide mutation is responsible for mutated Ras protein expression (see column 3). Ecker et al. teach incorporation of a 2'amino adenine at the position that is complementary to the uracil of the mutated codon serves to stabilize the hybridization of the antisense oligonucleotide to the mutated gene (see column 21, lines 40-45). Ecker et al. further teach incorporation of a 2, 6-diamino adenosine complementary to the uracil of the mutated codon was also found to be effective in increasing the hybridization of the antisense compound to the mutated gene (see column 21, lines 55-65).

Tuschl et al. teach target recognition is a highly sequence-specific process mediated by the siRNA complementary to the target and Tuschl et al. found that nucleotides in the center of the siRNA strand are important specificity determinants and even a single nucleotide change can reduce RNAi to undetectable levels. From this discovery, Tuschl et al. teach siRNA duplexes can discriminate between mutant or polymorphic alleles which are important in therapeutic developments involving said mutant alleles (see at least page 50). Tuschl et al. further disclose a method of

inhibiting the expression of a cellular gene that is a tumor gene (a mutant target gene), in vitro in a mammalian cell comprising introducing a dsRNA molecule and maintaining the cell for a time sufficient to obtain degradation of an RNA transcript (see page 7 lines 25-32 and page 8, lines 20-25). Tuschl et al. further disclose the dsRNA of their invention can be a 19-25 nucleotide duplex (see page 3, lines 22-26), the dsRNA has sufficient identity to a nucleic acid target molecule (see page 6, lines 7-11) and teach compositions comprising siRNA and an acceptable carrier (see page 9, lines 17-25). Tuschl et al. teach that siRNAs represent a new alternative to antisense or ribozyme therapeutics. Tuschl et al. teach the siRNA may contain at least one modified analogue, such as a modified base wherein the modified base comprises 5-bromouracil or 5-iodouracil and the dsRNA structures contain mismatches (page 4, lines 29-32 to page 5, lines1-3).

It would have been obvious to one of skill in the art to make a siRNA targeted to a dominant gain-of-function mutation, as taught by Tuschl et al. It would have further been obvious to incorporate modified bases as taught by Ecker et al.

At the time of filing of the instant application, it was well known in the art that dsRNAs were emerging as a more efficient technology for silencing gene expression. Hammond et al. teach two methods for silencing specific genes: antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "...questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach " "...dsRNAs have been shown to inhibit gene expression

in a sequence-specific manner" and further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression." Similarly, Bass et al. states that RNA interference using siRNA has "...repeatedly proven itself to be more robust than antisense techniques: It works more often, and typically decreases expression of a gene to lower levels, or eliminates it entirely." Bass et al. points out that siRNAs are effective at targeting transgenes as well as naturally occurring endogenous genes (see page 428). Bass et al. further states "...siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments."

Klug et al. has shown that targeting a gain of function mutant allele G93A and reducing expression from said allele is a promising therapeutic approach to treating ALS and because siRNAs were emerging as the new preferred class of inhibitory molecules to silence gene expression, it would have been obvious to make siRNA to target mutant alleles. One of skill in the art would have clearly looked to the teachings of Tuschl et al. to make siRNA given Tuschl et al. provide specific guidelines to make siRNA to any target gene and would have wanted to design a siRNA that is capable of distinguishing a mutant allele over the wild type gene given Tuschl et al. discloses that siRNA duplexes can discriminate between mutant or polymorphic allele.

Moreover, in efforts to improve the specificity of the siRNA to the mutant target gene, one would have wanted to make a siRNA wherein the antisense strand, the strand that binds to the target gene, comprises a modified base because Ecker et al. specifically teach incorporation of modified bases increase the specificity of the nucleic

acid to the mismatched base. One of skill in the art would have wanted to incorporate modifications to siRNA to improve the affinity for target genes because siRNA encounters similar problems as other nucleic acid based therapies such as antisense and a person of ordinary skill in the art has good reasons to pursue the known options, as taught by Ecker et al., within his or her technical ability.

Further, while the prior art do not teach mutant target genes wherein the point mutation is an adenine or thymine, Tuschl et al. do teach engineering siRNA to selectively target ant gene or mutant gene responsible for several disorders and based on the disease the specific point mutation could occur on an adenine or thymine and it would therefore be obvious and a matter of routine experimentation to design a siRNA targeted to said point mutations.

One of skill in the art would have had a reasonable expectation of success at targeting a gene responsible for disorders such as ALS given than Klug et al. has shown the G93A can be selectively targeted and inhibited using sequence specific inhibitory molecules and Tuschl et al. recognized siRNA were capable of discriminating between a mutant allele and wild-type allele. One would have expected to be able to incorporate a modified base into a siRNA and would have expected to be able to improve the target specificity.

Thus, in absence of evidence to the contrary, the invention would have been prima facie obvious to one of skill in the art.

Claims 2-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (cited on PTO Form 892 filed 11/15/2005) and Ecker et al. (US Patent No. 5,965,722 of record cited on PTO Form 892 filed 04/02/2007).

The claims are drawn to a siRNA comprising a sense strand and an antisense strand wherein the antisense strand comprises a modified base positioned opposite at least one pint mutation in the first allele and wherein the modified base is capable of enhancing binding interactions, wherein the sense strand comprises a sequence homologous to a mutant allele encoding a gain-of-function mutant protein, wherein the modified base is selected from the group as listed in claim 4, wherein the point mutation is an adenine or thymine, wherein the siRNA targets a disorder such as ALS, Huntington's, Alzheimer's or Parkinson's, wherein the siRNA is from 10-50, 20-40, 18-25 nucleotides in length an drawn to a composition and a host cell comprising said siRNA.

Xu et al. effectively demonstrates siRNA duplexes can discriminate between mutant and polymorphic alleles. Xu et al. teach siRNA that can selectively inhibit a mutant allele, G93A SOD1, while preserving expression of the wild-type gene with single-nucleotide specificity. Xu et al. teach that certain types of human disease, such as ALS, Huntington's disease, Alzheimer' disease or Parkinson's Disease are caused by dominant gain-of-function mutations and because the wild-type gene often performs important functions compared to the toxic effects of the mutant gene, it would be advantageous to selectively inhibit the mutated gene, particularly G93A SOD1 which is responsible for ALS (see Abstract and paragraph 0009). Xu et al. teach a method of

inhibiting the expression of a G93A in vitro in a mammalian host cell (see Examples). Xu et al. further disclose the siRNA of their invention can be a 10-50 nucleotide duplex, the siRNA may contain at least one modified analogue, such as a modified base wherein the modified base comprises 5-bromouracil or 5-iodouracil and teach compositions comprising siRNA and an acceptable carrier (see at least paragraphs 0038-0040 and 0089). Xu et al. do not teach the siRNA comprises modified based opposite the mutant allele and do not teach the SOD1 point mutations are adenine or thymine.

Ecker et al. teach sequence antisense compounds capable of discriminating between a mutated Ras gene as compared to the wild-type gene (see column 3) and teach that antisense compounds comprising modified nucleotide bases opposite the point mutation increase the affinity for base mismatches in mutated genes and further enhance the compounds selectivity for such mutated genes (see column 3). Ecker et al. teach a single nucleotide mutation is responsible for mutated Ras protein expression (see column 3). Ecker et al. teach incorporation of a 2'amino adenine at the position that is complementary to the uracil of the mutated codon serves to stabilize the hybridization of the antisense oligonucleotide to the mutated gene (see column 21, lines 40-45). Ecker et al. further teach incorporation of a 2, 6-diamino adenosine complementary to the uracil of the mutated codon was also found to be effective in increasing the hybridization of the antisense compound to the mutated gene (see column 21, lines 55-65).

It would have been obvious to one of skill in the art at the time the invention was made to incorporate modified bases as taught by Ecker et al.

In efforts to improve the specificity of the siRNA to the mutant target gene, one would have wanted to make a siRNA wherein the antisense strand, the strand that binds to the target gene, comprises a modified base because Ecker et al. specifically teach incorporation of modified bases increase the specificity of the nucleic acid to the mismatched base. One of skill in the art would have wanted to incorporate modifications to siRNA to improve the affinity for target genes because siRNA encounters similar problems as other nucleic acid based therapies such as antisense and a person of ordinary skill in the art has good reasons to pursue the known options, as taught by Ecker et al., within his or her technical ability. Moreover, while Xu et al. do no teach mutant target genes wherein the point mutation is an adenine or thymine, Xu et al. do teach engineering siRNA to selective target mutant alleles of several disorders and based on the disease the specific point mutation could occur on an adenine or thymine and it would therefore be obvious and a matter of routine experimentation to design a siRNA targeted to said point mutations.

One would have expected to be able to incorporate a modified base into a siRNA and would have expected to be able to improve the target specificity and would have clearly expected to be able to make a siRNA to target a mutant allele wherein the point mutation is an adenine or thymine given Xu et al. teach the steps to making any siRNA to target mutant genes.

Thus, in absence of evidence to the contrary, the invention would have been prima facie obvious to one of skill in the art.

Response to Applicant's Arguments

Applicant's arguments filed 01/12/2009 are drawn to rejections that have been withdrawn however as some of the same prior art references were used in the new grounds of rejection above, response is warranted. Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues the teachings of Ecker et al. are directed to antisense DNA oligonucleotides and nothing in the teachings of Ecker et al. suggest a need in the prior art for use of an alternative molecule for specific inhibition of expression of a mutant gene and nothing in Hammond et al. or Bass et al. would make up for the deficiencies of Ecker et al., particularly because neither teach siRNAs comprising modified nucleotides targeted to a mutant allele.

In response to Applicant's argument that one would not have been motivated to seek alternate molecules to antisense for specific gene, Ecker et al. teach a method of inhibiting a mutant gene using an inhibitory antisense nucleic acid molecule and given that both Hammond et al. and Bass et al. teach antisense compounds are less specific compared to siRNA for silencing gene expression, one of skill in the art would have clearly substituted siRNA inhibitory molecules for antisense molecules and would have clearly substituted siRNA molecules for antisense molecules as taught by Ecker et al. to silence mutant gene expression. One of skill in the art would have been motivated to

substitute the antisense compound taught by Ecker et al. with a more efficient inhibitory molecule for the sole purpose of targeting a mutant gene more efficiently and silencing gene expression of said mutant target gene more efficiently. Moreover, given that both the antisense compound and siRNA compound are designed to recognize a target gene through complementarity to the target gene, of skill in the art would be motivated to design an siRNA to a mutant target gene and have a reasonable expectation of success at being able to initiate gene silencing of a mutant target gene using a siRNA.

Further, it was well known at the time of filing of the instant invention regarding the desirability to target a mutant allele in a pair of alleles wherein the mutant allele is responsible for the progression of certain diseases, such as cancer and in do so provides a promising therapeutic approach to treating certain diseases and because siRNAs were emerging as the new preferred class of inhibitory molecules to silence gene expression, it would have been obvious to make siRNA to target mutant alleles

Hammond et al. and Bass et al. were relied upon to provide motivation to use a siRNA to inhibit gene expression compared to an antisense compound and were not relied upon to teach modifications of siRNA and therefore one of skill in the art would be motivated to substitute a siRNA for an antisense given that siRNAs have proven to be more target specific as discussed above.

Applicant's arguments regarding Tuschl et al. not teaching the structure and function of the claimed siRNA and Hojo et al. not teaching the use of siRNAs or any other molecule to direct cleavage are not convincing. Tuschl et al. teach the development of siRNA as a new alternative to antisense technology and therefore one

would have wanted to use this new technology which was proven to be more sequence specific and would have had a reasonable expectation of success at making a siRNA targeted to a mutant allele. Hojo et al. was relied upon to teach the obviousness of targeting a mutant cancer gene wherein the mutation responsible for mediating the disease is found on an adenine or thymine.

Applicant further argues one of skill in the art would not have had a reasonable expectation of success in using a siRNA to target a mutant allele because antisense and siRNA molecules operate through very different cellular mechanisms. Applicant states that it was recognized in the art that siRNAs containing a single base mismatch with the target RNA could effectively mediate RNAi silencing of the target gene and unlike the single nucleotide discrimination obtained with an antisense oligonucleotide, siRNAs are incapable of such single nucleotide discrimination between the wild type and mutant allele.

Applicant points to Boutla et al. and Caplen et al. for support that siRNAs were incapable of discriminating against single nucleotide mismatches. While Boutla et al. demonstrates siRNA with single nucleotide mismatches were still capable of inducing RNAi in whole organism, introduction of the single nucleotide mismatches did not silence the gene as efficiently as with no mismatches and Boutla et al. states that this observation will require a more detailed analysis to access at what position and to what degree sequence deviations can or cannot be tolerated (see page 1779). Caplen et al. does not specifically teach using siRNA with the capability of single nucleotide discrimination. Caplen et al. teach siRNA targeted to genes having a trinucleotide

expansion responsible for a dominant genetic disorder and showed promising results. Caplen et al. cautions that further studies need to be investigated but does in fact state their study demonstrates the feasibility of targeting disease associated transcripts. Therefore, one of skill in the art would not take from Caplen et al. that single nucleotide discrimination using siRNA would not be expected to work.

Thus, Applicant's argument regarding the incapability of siRNA to recognize and silence gene expression of mutant genes is not convincing. As evidenced by Xu et al. (cited in the Office action filed 04/02/2007 and discussed herein), siRNA are capable of allele specific gene silencing wherein the siRNA can selectively inhibit a mutant gene while preserving the expression of the wild-type gene. Xu et al. teach an effective method of using siRNA to treat genetic disorders associated with expression of gain of function proteins from a mutant gene. Thus, one of skill in the art would have clearly had a reasonable expectation of success at generating a siRNA to targeted to a mutant gene and clearly would have expected to be able to silence gene expression of a mutant target gene given Xu et al. specifically teach allele-specific targeting using a siRNA. Applicant states they will consider filing a declaration evidencing that the instant invention was made prior to Xu et al. and Xu et al. would not be available as prior art and as a result, there was no reasonable expectation of success as using siRNA in single nucleotide discrimination before the instant invention. Because Applicant's have not filed a declaration and made the declaration of record, Xu et al. is still available as prior art.

Re: Claim Rejections - 35 USC § 103

The rejection of claims 2-8 and 10-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ecker et al. (US Patent No. 5,965,722), Hojo et al. (Eur Respir J, 1998), Hammond et al. (Nature Reviews Genetics, 2001), Bass et al (Nature, 2001) and Tuschl et al. (cited on PTO Form 892 filed 11/15/2005) is withdrawn in view of the new grounds of rejection above.

The rejection of claims 2-5, 7 and 9-17 under 35 U.S.C. 103(a) as being unpatentable over Ecker et al. (US Patent No. 5,965,722), Hammond et al. (Nature Review Genetics, 2001), Bass et al (Nature, 2001) and Tuschl et al. (cited on PTO Form 892 filed 11/15/2005) and Xu et al. (cited on PTO Form 892 filed 11/15/2005) is withdrawn in view of the new grounds of rejection above.

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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Kimberly Chong/
Primary Examiner
Art Unit 1635